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EXAMINER	
SALMON, KATHERINE D	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,224	RUSSELL ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-10,12,13,15,18,20-27,40,47 and 48* is/are pending in the application.

4a) Of the above claim(s) *18 and 20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-10,12,13,15,40,47 and 48* is/are rejected.

7)☒ Claim(s) *1, 6-10, 12-13, 15, 40, and 47-48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/10,10/25/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 1/5/2011 and the arguments set forth on 10/25/2010.

2. Claims 1, 6-10, 12-13, 15, 18, 20-27, 40, and 47-48 are pending. Claims 2-5, 11, 14, 17, 19, 28-39, 41-46, and 49-55 have been cancelled.

3. This application contains claims 18, 20-27 drawn to an invention nonelected with traverse in the reply filed on 1/04/2010. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. The following rejections for Claims 1, 6-10, 12-13, 15, 40, and 47-48 have been modified to take into account the amendments to the claims or reiterated. Response to arguments follows.

5. This action is FINAL.

Withdrawn Objections and Rejections

6. A. The priority and oath deficiently issue presented in sections 5 and 6 of the previous office action are moot based upon the submission of the ADS filed 10/25/2010 and the correction of the oath filed 10/25/2010.

B. It is noted that the legible copies of the nonpatent literature discussed in section 7 of the previous office action have been received and are cited on the IDS filed 4/29/2010.

C. The objection to the specification made in section 9 of the previous office action has been withdrawn based upon clarification of the record made in section IV of the reply.

D. The objection to the claims made in section 10 of the previous office action is moot based upon amendments to the claims or cancellation of the claims.

E. The 35 USC 101 rejection made in section 11 of the previous office action is moot based upon amendments to the claims.

F. Although the 35 USC 112/2nd rejection is being maintained, as discussed below. The issue with regard to the term "critically ill", “severe” and “less severe” made in section 12 of the previous office action is withdrawn after further consideration.

G. The rejection of the claims under 35 USC 112/1st Written Description made in section 14 of the previous office action is moot based upon amendments to the claims.

H. The rejection of the claims under 35 USC 102(b) made in section 16 of the previous office action is moot based upon amendments to the claims.

Information Disclosure Statement

7. The information disclosure statement (IDS) submitted on 4/29/2010 and 10/25/2010 have been considered by the examiner.

Newly Applied as necessitated by amendment- *Claim Objections*

8. Claims 1, 6-10, 12-13, 15, 40, and 47-48 are objected to because of the following informalities: Claim 1 recites “polymorphic position 201 of SEQ ID NO 1 which genotype is” which is grammatically incorrect. It is suggested that the claim be amended to “polymorphic position 201 of SEQ ID NO 1 wherein the genotype is” Appropriate correction is required.

Reiterated- *Claim Rejections - 35 USC § 112/2nd paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 6-10, 12-13, 15, 40, and 47-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6-10, 12-13, 15, 40, and 47-48 are indefinite. The terms "enhanced recovery" and “enhanced ability” in claim 1are a relative terms which render the claim indefinite. The term "enhanced" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically it is not

clear the degree of recovery which is required to be “enhanced”. For example it is not clear if recovery at a normal rate of time would be considered “enhanced”. As such the metes and bounds of the claim are not clear.

The term "poor” in claim 8 is a relative term which renders the claim indefinite. The term "poor" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically it is not clear which outcomes would be considered poor outcomes. For example having a treatable disease condition would be considered a poor outcome compared to not having a disease, but having an untreatable disease condition would also be considered a poor outcome. As such it is unclear the degree of a "poor" outcome which must be observed to be considered within the metes and bounds of the claims.

Response to Arguments

The reply traverses the rejection. A summary of the arguments made in the reply is provided below with response to arguments following.

A. The reply presents a summary of the rejection (p. 9-10 2nd paragraph). The reply asserts that the use of these terms would be understood by a person of skill in the art as the application on p. 22-25 describes the systems of APACHE II scoring and Bressels scoring to determine a patient’s outcome or prognosis (p. 10 3rd paragraph).

These arguments have been fully reviewed and have been partially found persuasive.

It is noted the descriptor found on p. 22-25 of the instant specification provides guidance to the skill artisan to determine the metes and bounds of severe, less sever, and critically ill. However, it does not provide guidance to determine the metes and bounds of the terms “poor” and "enhanced recovery". As such these arguments have not overcome the indefiniteness of these terms presented above.

B. The reply asserts that similar claim languages have been used in an allowable claim (p. 10 3rd paragraph and pointing to Claim 1, 11, and 14 of US Patent Application 10/515493).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that patent applications are examined on a case by case basis and therefore language which may be acceptable in one application may not have sufficient support in another case. However, with regard to the cited claims from US Patent Application 10/515493 it is noted that this case does not provide claims which recite enhanced recovery or poor outcome and as such are not commensurate in scope. Rather, the allowed claims show correlations of an increased or decreased ability to recover as compared to a patient with a specific genotype. As such the allowed claims are towards a different phrase (e.g. ability to recover vs. enhanced ability) and required a comparison step. Herein in the instant case, there is no standard for ascertaining which recovery rates would be considered "enhanced" or “poor”.

Modified based upon Amendments- Claim Rejections - 35 USC § 112/Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 6-10, 12-13, 15, 40 and 47-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (A) A method for determining an increased risk of developing gram positive sepsis infection or gram positive SIRS infection comprising obtaining a sample from a human patient, determining the genotype at position 201 of SEQ ID No. 1 in the patient is an AA genotype, wherein the presence of AA indicates that the patient has an increased risk of developing gram positive sepsis infection or gram positive SIRS infection compared to patients who have an AT or a TT genotype at position 201 of SEQ ID NO. 1. (B) A method for determining a decrease survival in a human patient infected with gram positive sepsis comprising obtaining a sample from a human patient who has systemic inflammatory response syndrome (SIRS), determining the genotype at position 201 of SEQ ID No 1 in the patient is a AT or TT, wherein the presence of AT or TT indicates that the patient has a decreased survival as compared to a patient who has an AA genotype, does not reasonably provide enablement for a determination of prognosis in any subject of enhanced recovery with any type of SIRS, sepsis, septic shock (e.g. gram positive or gram negative) by determining any genotype at position 201 of SEQ ID NO. 1. The claims further are drawn to prediction or indication of any severe or less

severe cardiovascular or respiratory dysfunction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The breadth of the claims

The claims encompass a correlation of prognosis in a subject of enhanced recovery from an inflammatory condition or increased risk of developing a gram positive infection, SIRS, sepsis, or septic shock by detecting a genotype at position 201 of SEQ ID NO. 1. The claims are drawn to a protective genotype being predictive or indicative of enhanced ability to recover from the inflammatory condition or gram positive infection and a risk genotype being predictive or indicative of an increased risk for developing the inflammatory condition or gram positive infection.

The claims are drawn to correlations of the homozygous T genotype at position 201 of SEQ ID No. 1, the T allele at position 201 of SEQ ID NO.1 and the A allele at position 201 of SEQ ID No. 1.

The claims are drawn to determining in critically ill subjects that association of the

presence of protective or risk genotypes and severe or less severe cardiovascular or respiratory dysfunction.

As discussed below, although the specification is enabling for the specific scope of a particular SNP with a particular disease condition, the specification does not provide guidance for the breadth of the claims. Specifically the claims are towards prognosis of enhanced recovery or risk of developing an inflammatory condition by determining any genotype of at positive 201 in SEQ ID No 1. As discussed below, the specification does not provide guidance for such breadth. Further the art discloses that such associations are species, diseases, and genotype specific. As such, the associations made in one particular correlation would not be predictive in for any other correlation.

Nature of the Invention

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification

The specification asserts that systemic inflammatory response syndrome (SIRS) is characterized by increased inflammation, increased coagulation, and decreased fibrinolysis (p. 1 lines 18-25). The specification asserts that Toll-like receptor 2 (TLR-2) has an important role in response to gram-positive bacteria (p. 1 lines 24-26).

The specification discloses that human TLR-2 maps to chromosome 4 and

extends over 2.6 kb (p. 2 lines 11-15). The specification asserts that one particular SNP is found at position 201 of SEQ ID No. 1 which represents a SNP that corresponds to -16934 relative to the TLR-2 transcriptional start site (p. 2 lines 12-20).

The specification asserts that identification is based upon the association with a decreased likelihood of recovery from an inflammatory condition (i.e. risk genotype) or an increased likelihood of recovery form an inflammatory condition (i.e. protective genotype) (p. 3 lines 6-10). However, these associations must be individually examined to determine if a particular genotype would be considered a risk, a protective, or a neutral genotype. The specification asserts that the risk genotype may be an indication of an increased risk of not recovering from an inflammatory condition and can including at least one T nucleotide at position 201 of SEQ ID NO. 1 (p. 9 lines 5-9). However, although there appears to be asserted associations of having an AT or TT and a decrease survival (p. 45 lines 1-5) not all associations to survival have been validated. Specifically Sutherland et al. (as discussed below) teaches that the genotype of AA at position 201 of SEQ ID No. 1 was not associated with survival. As such the art teaches that although some correlations might be predictive, the breadth of the claims is not predictable. Specifically even when the skill artisan examines only one polymorphic position of TLR2, the associations of the genotypes and inflammatory conditions can be directly extrapolated to one another.

Further, even at the site of position 201, the claims would encompass associations to three genotypes, AA, AT, and TT, and prognosis, recovery, or increased risk of developing an inflammatory condition. These associations must each be

evaluated individually and the correlation of one association is not predictive of the correlation of any other association. In particular, as described in the paragraph above, and association of AT or TT with survival does not provide guidance that the genotype of AA is associated with survival. Specifically, even though the specification provides guidance that there is an association with decreased survival and AT or TT, the art (Sutherland et al), teaches there is no association between survival and AA.

The claims are further drawn to broad terminology in which the specification has not provided any particular associations. The claims are drawn to "enhanced recovery". This term is not defined in the specification and it is not clear the difference between recovery and enhanced recovery. As such enhanced recovery would not only encompassed recovery from an inflammatory condition, but recover at a quicker pace. The specification has not provided guidance to determine if any of the polymorphic sites of TLR-2 are predictive of such a phenotype. Further, such an analysis would require many rounds of experimentation without a guarantee of success.

Working Examples

The specification does not provide a working example of the breadth of the claims, but rather, teaches correlations between particular inflammatory conditions and particular genotypes in a human patient.

Example 1 provides the haplotype of 223 patients who had at least two criteria for sepsis (p. 41 liens 19-21). The specification provides different associations based upon this study.

Association 1. Increased rate of sepsis upon admission to the study (p. 43 lines 1-9).

The specification asserts that patients with a homozygous A genotype at position 201 had a relative risk of 1.3 of having sepsis on day 1 (95% CI= 1.1-1.6). This association appears to indicate that the rate of sepsis is increased in patients with AA genotypes as compared to patients with AT or TT genotypes. However, this association is not clear as it is not clear what phenotype is being examined by the specification. The specification asserts that there were more patients with the genotype of AA who had sepsis on day one of the observation period (p. 43 lines 1-5); however, it appears that all of the 223 patients have at least 2 or the 4 SIRs criteria for sepsis (p. 42 lines 23-27). The instant specification defines sepsis as the presences of at least two SIRS criteria (p. 21 lines 29-31). As such it appears that all the patients would be defined as having sepsis at the point of admission, regardless of the genotype.

Association 2. Association with predictive occurrence of gram positive cultures (p. 43 lines 10-22).

The specification asserts that patients homozygous for the A allele were twice as likely to have a gram positive culture as oppose to patients with AT or TT (RR=2.0, 95% CI=1.1-3.4). As indicated by the scope of enablement provided above, this association appears to be predictive. Further it is noted that post filing art of Sutherland et al., as discussed below, further confirmed this association.

Example 2 proves that the SNP position at 201 of SEQ ID No. 1 was examined in a cohort of 638 patients with SIRS (p. 44). The specification provides associations

based upon this detection.

Association 3. Progressive decrease of survival

The specification asserts that there was a significant progressive decrease of survival in patients who were AA vs. AT or TT (p=0.0359). The specification asserts that patients with AT or TT had a decrease in survival versus patients with AA (p. 45 lines 1-5). As indicated in the scope of enablement, this association appears to provide a predictive correlation between patients with AT or TT genotypes and survivability. Although, Sutherland et al, discussed below, teaches that AA is not associated with increase survivability.

Association 4. Prevalence of sepsis on admission

The specification asserts that there was a progressive increase in prevalence of sepsis on admission to the ICU in patients who have TT, AT, and AA genotypes (p. 46 lines 1-5). However as discussed above, it appears that all the patients in the study had sepsis and therefore it is not clear what this association is towards.

Association 5. Days alive

The specification asserts that there was a significant association of T/A with days alive and free of cardiovascular dysfunction (p=0.019). An association with days alive and free of vasopressors (p=0.019) Days alive and free of inotropic agents (p=0.074) (p. 46 lines 1-15). The specification discloses that patients who carried AT or TT had more cardiovascular dysfunction shown as fewer days alive and free of cardiovascular dysfunction, vasopressor use and inotropic agent use (p. 46 lines 1-15). The specification asserts that therefore patients with SIRS having a risk genotype (e.g.

having a T allele) have an increase in cardiovascular dysfunction (p. 46 lines 6-15). Although the specification appears to show a correlation between the T alleles and cardiovascular dysfunction. The specification does not provide a validation study of this association. Further, study of this position and this phenotype indicates that this association is unpredictable. In particular Sutherland et al. teaches that there was no association of AA with septic shock or survival (discussed below). Sutherland further teaches that septic shock is defined by sepsis pulse significant hypotension or the need for vasopressors. As such the lack of an association with septic shock indicates that there is no association with the cardiovascular dysfunction or vasopressors associated with the phenotype.

Association 6. Days alive and free of 3 of 4 SIRs criteria

The specification asserts that there was a trend towards this association of patients with the T alleles (p=0.095) (p. 46 lines 17-20). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 7. Days alive and free of coagulation

The specification asserts that there was an association between A/T genotype and days alive and free of coagulation (p=0.048). The specification asserts that patients who carried the AT or TT had coagulation dysfunction shown in fewer days alive and free of coagulation dysfunction (p. 47 lines 1-2). Although the specification appears to show a correlation between the T alleles and cardiovascular dysfunction. The

specification does not provide a validation study of this association. Further, study of this position and this phenotype indicates that this association is unpredictable. In particular Sutherland et al. teaches that there was no association of AA with septic shock or survival (discussed below). Sutherland further teaches that septic shock is defined by sepsis pulse significant hypotension or the need for vasopressors. As such the lack of an association with septic shock indicates that there is no association with the cardiovascular dysfunction or vasopressors associated with the phenotype.

Association 8. Days alive and free of renal support and hepatic dysfunction

The specification asserts that there is a trend towards an association of renal support and days alive (p=0.082) and free of hepatic dysfunction (p=0.035) (p. 47 lines 1-10). Such that patients who carried the T allele had more hepatic dysfunction shown as fewer days alive and free of hepatic dysfunction (p. 47 lines 1-10). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Sepsis subgroup: The specification discloses that the T/A polymorphism was examined in 513 critically ill patients who had sepsis (p. 47 lines 10-20)

Association 9. The specification asserts that there was a trend toward a progressive decrease in 28 day survival amount AA, AT, TT genotypes groups (p=0.089) (p. 48 lines 4-5). It is noted that this association is not statistically significant. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype. Therefore this indicates that the combination of AA,

AT, and TT does not provide a clear determination of survivability. Both the specification and the art indicates that there is only a predictive association to decrease survival with the detection of AT and TT as compared to AA individuals.

Association 10. Days alive and free of vasopression (p=0.049) and cardiovascular dysfunction (p=0.041), therefore patients who had sepsis and carried the T allele had more cardiovascular dysfunction shown as fewer days alive and free of cardiovascular dysfunction and vasopressor use.

Association 11. Trend of association of Days alive and free of 3 out of 4 SIRS criteria (p=0.082) and days alive and free of steroid support (p=0.092) (p. 49 lines 8-13). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 12. Trend for days alive and free of coagulation (p=0.084), free of INR (p=0.06), and free of hepatic dysfunction (p=0.066) (p. 49 lines 14-19). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

Association 13. Trend between the genotype and days alive and free of respiratory dysfunction (p=0.071), free of mechanical ventilation (p=0.0999) (p. 49 lines 20-26). It is noted that this association is not statistically significant nor has it been validated. Therefore the specification has not provided a clear predictive association between this particular phenotype and genotype.

The unpredictability of the art and the state of the prior art

The art teaches that the association of particular polymorphic regions and sepsis is specific to the type of sepsis. Woehrle et al. (Cytokine 2008 VOl. 41 p. 322) that of the 325 patients with sepsis and septic shock associated with gram positive bacteria, none were positive to the SNP Arg677Trp (p. 324 2nd column 4th paragraph). Woehrle et al. teaches that association of SNPs and sepsis might be bacteria type dependent. Woehrle et al. teaches that Arg753Gln heterozygous patients were associated with Candida included sepsis but not Gram-positive sepsis (p. 328 1st paragraph). As such the type of sepsis (e.g. which bacteria the sepsis is from) would effect the correlation of the phenotype to the genotype. Specifically in this case, the associations of the particular polymorphic position were observed in gram positive sepsis.

Post-filing art teaches that even with the specific polymorphic position of 201 of SEQ ID No. 1 each association to inflammatory condition must be individually examined and validated. Sutherland (Crit Care Med 2005 VOl. 33 p. 638) teaches that patients were used which had at least 2 of the 4 SIRs criteria and therefore were considered critically ill (p. 639 2nd column 2nd paragraph). Sutherland et al. teaches that these patients were genotyped for polymorphisms in TLR2 (p. 639 2nd column 3rd paragraph). Sutherland et al. teaches the detection of the same SNP region as the instant specification (-16933 T/A SNP) (p. 640 1st paragraph). Sutherland et al. teaches that TLR2 -16933AA was associated with significant increased prevalence of sepsis on admission to the ICU ($p < 0.03$ Figure 7) and specifically with increased prevalence of

Gran positive infections (p=0.04) (p. 641 1st column last paragraph-2nd column 1st paragraph). Sutherland et al. teaches that AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd column 1st paragraph). The association to prevalence of sepsis on admission to the ICU is still unclear in the art as it is not clear what defines a patient as having sepsis. Sutherland et al. teaches that the patients admitted all had at least 2 or the 4 SIRs criteria. Sutherland et al. teaches that Sepsis was defined as the presence of two or more SIRS criteria plus the presence of a known or suspected infection during the 24 hour period (p 639 3rd column 2nd paragraph). Therefore it appears that having two or more SIRS criteria defines the whole population studies as having sepsis.

Sutherland et al. teaches that septic shock was defined by sepsis plus significant hypotension such as systolic blood pressure or the need for vasopressors (p. 639 3rd column 3rd paragraph). Sutherland et al. teaches that AA was not associated with increased prevalence of positive bacterial cultures or septic shock on admission to the ICU or with a significant difference in 28 day survival (p. 641 2nd column 1st paragraph).

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Quantity of Experimentation and Conclusion

The quantity of experimentation in this area would be extremely large since there is significant number of parameters that would have to be studied. The claims are

drawn to associating any genotype at position 201 of SEQ ID NO. 1 with enhanced recovery or increased risk of developing gram positive infection, sepsis, SIRS, or septic shock. Therefore the claims encompass the association of any genotype (AA, AT, TT) with enhanced recovery or increased risk, however, the specification only provides specific associations between individual genotypes and a phenotypic response.

To practice the invention as broadly as it is claimed, the skilled artisan would have to determine associations within any type of sepsis, SIRs, or septic shock type and determine the association of each of the genotypes with recovery or increased risk. The skilled artisan would need to perform undue experimentation to determine such an association.

Further, the art indicates that these experimentations do not have a guarantee of success Woehrle et al. teaches that associations to sepsis are further bacteria type dependent. Sutherland teaches that even at the specific position of 201 of SEQ ID No. 1 and gram positive sepsis, each association must be evaluated to determine if there is a predictably statistically significant association.

Thus the applicants have not provided sufficient guidance to enable a skilled artisan to make the claimed invention in a manner reasonably correlated with the claimed method.

Therefore the method as claimed would require a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the negative teachings in the art, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that

it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The reply traverses the rejection. A summary of the arguments made in the reply is provided below with response to arguments following.

A. The reply summarizes the rejection and amendments to the claims (p. 11 and p. 12 1st paragraph). The reply asserts that SIRS, sepsis, and septic shock have been defined in the specification at p. 21 (p. 12 2nd paragraph). The reply asserts that Bone et al. (Chest 1992 found on the IDS of 10/25/2010) further shows that same definition of sepsis (p. 12 last paragraph). The reply asserts that Bone further defines sever sepsis and septic shock (p. 13 1st full paragraph). The reply asserts that therefore anyone with sepsis or suffering from septic shock suffers from SIRS (p. 13 2nd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Regarding the inflammatory conditions the response asserts that the specification provides enabling support for sepsis, septic shock, or SIRS. The response asserts that anyone with sepsis or septic shock suffers from SIRS. This argument has been considered but is not found fully persuasive. In the instant case the specification states that SIRS can include sepsis and septic shock however the specification states that sepsis and septic shock are distinctly different. Sepsis is defined as at least two SIRS criteria and known or suspected source of infection. Septic shock is defined as sepsis plus at least one organ failure. A SIRS diagnosis does not require a known or suspected source of infection or an organ failure and as such one can have SIRs but

not have septic shock. Further one can have sepsis without having septic shock as having sepsis does not require having at least one organ failure. As such it is noted that the scope of enablement provided above can include a determination of SIRs from gram positive sepsis infected patient with the same associations as provided with a gram positive sepsis individuals as these terms appear to be equivalent. However, the term septic shock requires a further analysis of organ failure. As discussed above Sutherland et al. teaches that patents with AA are not associated with a determination of septic shock. Further, the specification has not provided a predictable correlation between septic shock and any genotype at position 201 of SEQ ID No. 1. Herein in the instant case the claims are drawn to associating a protective genotype at polymorphic position 201 of SEQ ID No. 1 with enhanced ability to recover form gram positive infection, SIRS, sepsis, and septic shock and a risk genotype as conveying an increased risk of developing gram positive infection, SIRS, sepsis, or septic shock. As discussed in the Scope of enablement above the specification has not provided guidance to predictably determine which genotypes are protective and which ones are risk genotypes for gram positive infection, SIRS, sepsis, or septic shock for the encompassed genotypes.

B. The reply asserts that Sutherland was an after filing publication which was conducted by the present inventors on a smaller patient cohort (p. 14 last three paragraph). The reply asserts that it is not clear why the larger patient cohort was not reported, but the results of the larger study in the instant specification is a better

representation of the prognostic significations of the polymorphisms at this site of the TLR2 gene (p. 15 1st paragraph).

These arguments have been fully reviewed but have not been found persuasive.

The reply appears to be arguing that the data provided in the specification is more predictive of a general human population and the association of genotypes at position 201 of SEQ ID No. 1 than Sutherland et al., however, these are arguments of counsel.

As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, *
(3) after final rejection **>, but before or on the same date of filing an appeal, upon a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented in compliance with 37 CFR 1.116(e); or
(4) after the prosecution is closed (e.g., after a final rejection, after appeal, or after allowance) if applicant files the affidavit or other evidence with a request for continued examination (RCE) under 37 CFR 1.114 in a utility or plant application filed on or after June 8, 1995; or a continued prosecution application (CPA) under 37 CFR 1.53(d) in a design application.

For affidavits or declarations under 37 CFR 1.132 filed after appeal, see 37 CFR 41.33(d) and MPEP § 1206 and § 1211.03.

Further, it is noted that Sutherland et al. was provided to show that at the time of filing it was unpredictable that any genotype at position 201 of SEQ ID No. 1 is associated with enhanced recover from or increased risk of developing any type of SIRS, sepsis, or septic shock (e.g. gram positive or negative). Specifically the specification teaches that there is only a trend (p=0.089) between recovery and AA at position 201 (Association 9 p. 48). Therefore the specification does not provide a predictably associated p value and then even after filing this association has not been reliably produced (as indicated by Sutherland et al). As such neither the specification nor the art provides guidance for the predictable association of any genotype at position 201 to SIRS, sepsis, or septic shock as this trend shown in the specification has not been found to be predictable.

C. The reply asserts that it appeared that the Office tended not to accept that a trend is predictive or of prognostic value (p. 15 2nd full paragraph). The reply points to Khazanie et al. (cited on the IDS of 10/25/2010) which state p-values serves as a measure of the strength of the justification for rejecting the null hypothesis and should not be viewed as an absolute value (p. 15 2nd paragraph). The reply asserts that a Rule 132 declaration from a statistician can be submitted for further support (p. 15 3rd paragraph). The reply asserts that there is no law that requires a stricture cutoff value of significant to be p less than 0.05 (p. 15 3rd paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Although the examiner agrees that there is no law that requires a statistically significant p value, in so far that the specification has a diagnostic robust and reliable

relationship it is critical and essential to show the skilled artisan that the use of the claimed invention is predictable. Diagnostic associations are unpredictable and as such require guidance to show a robust relationship. Pvalues are scientific convention of showing a reliable association. Herein in the instant case, the trend provided by the specification has been shown not to be a reliable and robust association (see discussion with regard to Sutherland in part b of response to arguments). As such although a p value is not absolutely required by law, the instant specification has not provided a robust association which will enable the skilled artisan to make and use the method as claimed.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday - Friday 9AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
Examiner, Art Unit 1634